

## Increasing Incidence of Severe Epstein-Barr Virus-Related Infectious Mononucleosis: Surveillance Study

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**Older patients are more susceptible to severe Epstein-Barr virus (EBV)-related infectious mononucleosis (IM). This condition may increase in industrialized countries where primary EBV infection occurs later in life. Between 1990 and 2004, 38 patients were admitted to our department with EBV-related IM. Two patients died. The annual incidence increased significantly ( $r = 0.623$ ;  $P = 0.013$ ).**

Primary Epstein-Barr virus (EBV) infection during childhood is usually subclinical, whereas infection of adolescents or adults results in infectious mononucleosis (IM) in 30 to 70% of cases and can prove severe (1, 2, 5, 6, 8). We recently noticed a sharp increase in the incidence of EBV-related IM that required hospitalization.

Pontchaillou is a university-affiliated hospital which serves as a referral center for patients more than 15 years old in our area. EBV-related IM was defined as IM with at least one serological marker of acute EBV infection among the following: (i) the presence of immunoglobulin M antibodies to viral capsid antigen in the absence of antibodies to EBV nuclear antigen (EBNA), (ii) the presence of heterophile antibodies (Monospot or Paul-Bunnell Davidsohn test), and/or (iii) a positive PCR for EBV DNA. Patients previously known as immunocompromised were excluded. Linear trends over time were analyzed by a nonparametric Spearman rank order correlation analysis, using years as the independent variable.  $P$  values were based on two-tailed tests of significance ( $P < 0.05$ ). Statistical analysis was performed using SPSS software version 11.5 (SPSS).

Between 1990 and 2004, 38 patients (15 male, 23 female) were admitted to our department with EBV-related IM. The mean age was 22.6 years (standard deviation, 9.2 years; range, 16 to 53 years). Patients were admitted because of severe hepatitis ( $n = 12$ ), severe dysphagia ( $n = 8$ ), hemophagocytic lymphohistiocytosis (HLH) ( $n = 5$ ), painful enlarged spleen ( $n = 4$ ), airway obstruction ( $n = 3$ ), meningoencephalitis ( $n = 3$ ), or myocarditis, hemolytic anemia, or pleural effusion (one patient each). The maximal temperature was  $>38^{\circ}\text{C}$  in 35 patients (92.1%), with a mean of  $39.7^{\circ}\text{C}$ . Pharyngitis was observed in 29 patients (76.3%); it was exudative in most patients ( $n = 23$ ). Other common findings were lymphadenopathy (71.1%), splenomegaly (44.7%), hepatomegaly (31.6%), jaundice (31.6%), and rash (28.9%). Atypical lymphocytes were observed on blood smears in 34 patients (89.4%). The white blood cell count was  $>8,000/\text{mm}^3$  in 26 patients (68.4%), with a mean of  $13,470/\text{mm}^3$  (range, 2,500 to 64,900). Thirteen pa-

tients (34.2%) had anemia, 10 (26.3%) had thrombocytopenia (platelet count of  $<150,000/\text{mm}^3$ ), and 33 (86.8%) had elevated aspartate aminotransferase and/or alanine aminotransferase. The median durations of fever and hospital stay were, respectively, 16.5 and 6 days (means were 22.5 and 10.7 days, respectively). Of 19 patients (50%) who received systemic corticosteroids, 5 received other immunomodulating treatment: intravenous immunoglobulins (IVIG) ( $n = 5$ ) and cyclosporine ( $n = 3$ ), rituximab ( $n = 1$ ), or antilymphocyte serum ( $n = 1$ ). Nine patients (23.7%) received antiviral treatment: foscavir ( $n = 5$ ), acyclovir ( $n = 2$ ), or valacyclovir ( $n = 2$ ).

From 1990 to 2001, the incidence of severe EBV-related IM was stable, with a mean of 1.4 admissions/year and only one patient admitted to the intensive care unit (ICU). During the years 2002 to 2004, 21 patients were admitted, including 8 to the ICU, of whom 2 died (Fig. 1). The annual incidence increased throughout the study period ( $r = 0.623$ ;  $P = 0.013$ ). The first patient who died was a 17-year-old male admitted in 2002 because of tonsillar enlargement causing airway compromise. He developed uncontrolled diffuse lymphoproliferation despite receiving corticosteroids, IVIG, cyclosporine, and rituximab. No clonal lymphoproliferation was identified in his peripheral blood, bone marrow smears, or lymph node biopsy despite repeated analysis by morphological examination, flow cytometry immunophenotyping, and molecular biology. The patient died with bulky enlarged lymph nodes, multiple-organ failure, and invasive aspergillosis. Testing for the genetic defect described for the X-linked lymphoproliferative syndrome was negative. The second patient who died was a 20-year-old woman admitted in 2003 for pancytopenia and severe hepatitis. On day 3, she developed HLH and died after 7 days of refractory multiple-organ failure despite treatment with foscarnet, corticosteroids, IVIG, cyclosporine, and antilymphocyte serum.

We observed a significant increase in the incidence of EBV-related IM requiring hospitalization. Potential biases include a lower threshold for hospitalization during recent years following our dreadful experience with a young patient who died after 1 month of intensive care in 2002. However, all patients presented with objective signs of severe IM, and hospitalization was clearly indicated for most, if not all, of them. More-

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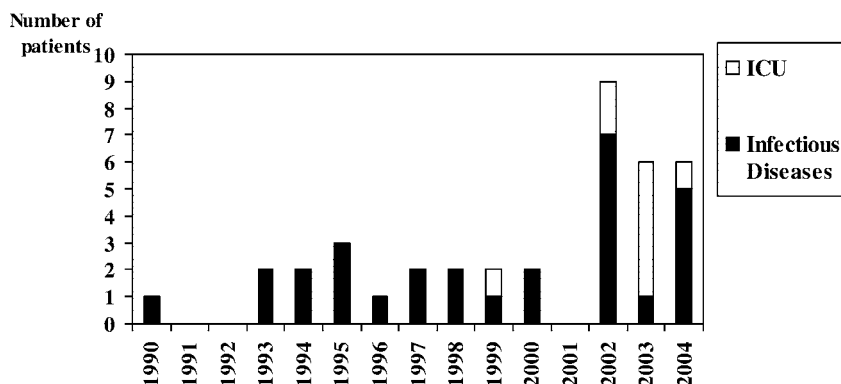


FIG. 1. Numbers of patients admitted for EBV-related infectious mononucleosis in a department of infectious diseases and an ICU (1990–2004).

over, recent studies from different settings showed similar patterns: the incidence of IM requiring hospitalization for adolescents and young adults significantly increased in England during the years 1989 to 1998, but the database did not allow us to distinguish between different causes of IM (7). In Israel, during the years 1988 to 1991, 85% of 590 young adults with clinically suspected IM were hospitalized during their illness (3). Theories for the emergence of severe EBV-related IM in adolescents and young adults in industrialized countries include better personal hygiene, improved public sanitation, and decreasing family sizes, all factors that delay primary EBV infection (8, 9). Falling childhood infection rates have resulted in an increase in the number of teenagers who are susceptible to a severe case of IM.

No published data suggest that a shift in the virulence of EBV has occurred. In this study, the most frequent clinical findings were those of the classical triad (fever, sore throat, lymphadenopathy), but our results differ somewhat from earlier studies of EBV-related IM (3, 5, 8). Specifically, differences were noted in the rate of lymphadenopathy (71.1% versus 88 to 100% in earlier reports), splenomegaly (31.6% versus 41 to 100%), and jaundice (31.6% versus 16.7% or less). Laboratory findings are in the range of previous reports, with atypical lymphocytosis (89.4% versus 20 to 100%), elevated liver enzymes (86.8% versus 50 to 90%), and atypical lymphocytes (68.4% versus 46 to 90%) being the most frequent. There are few data on the treatment of severe IM. It has been postulated that symptoms may be due to EBV-induced polyclonal humoral and cellular immunoreactivity and that only limited pathology is caused by viral replication (5, 8). A double-blind study showed that acyclovir has no significant effect on clinical symptoms of EBV-related IM (10). The combination of acyclovir and prednisolone did not affect the duration of symptoms or development of EBV-specific cellular immunity (11). Corticosteroids may be helpful in treating complications of IM,

including central nervous system involvement, myocarditis, tonsillar enlargement causing airway obstruction, and hemolytic anemia (5). Of note is that a retrospective study suggested that etoposide could be the treatment of choice for EBV-associated HLH (4).

The study presented herein is limited because it was retrospective, from a single department, and had a small sample size. However, an increase in the incidence of severe EBV-related IM may be expected in industrialized countries, since (i) primary EBV infection occurs there later in life and (ii) older patients are more susceptible to severe EBV-related IM.

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